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Trends in Major Lower Limb Amputation Related to Peripheral Arterial Disease in Hungary: A Nationwide Study (2004—2012)

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WHAT THIS PAPER ADDS

The study is the first nationwide report on PAD-associated lower limb major amputation trends from Hungary, showing an alarmingly high level of amputation and no significant change over a 9 year period (2004—2012). It provides amputation incidence data with external standardization to the European Standard Population (ESP) 2013 to ensure international comparability. The different age and sex composition of the countries can be monitored in a way that avoids a demographics related bias in comparisons. This method has not been widely used in the amputation literature to date. The high and constant level of amputation incidence data, based on an international comparison of cardiovascular risk profiles, is presumably related to the lack of vascular services. The characteristics of this relationship must be clarified in future analysis.

Objectives: To assess the trends of peripheral arterial disease associated major lower limb amputation in Hungary over a 9 year period (2004—2012) in the whole Hungarian population.
Methods: This was a retrospective cohort study employing administrative health care data. Major amputations were identified in the entire Hungarian population during a 9 year period (2004—2012) using the health care administrative data. Direct standardization was used to eliminate the potential bias induced by the different age and sex structure of the compared populations. For external direct standardization, the ESP 2013 was chosen as reference.
Results: 76,798 lower limb amputations were performed. The number of major amputations was 38,200; these procedures affected 32,084 patients. According to case detection, 50.4% of the amputees were diabetic. The overall primary amputation rate was 71.5%. The annual crude and age adjusted major amputation rates exhibited no significant long-term pattern over the observation period. The major lower limb amputation incidence for the overall period was $42.3/10^5$ in the total population and $317.9/10^5$ in diabetic population.
Conclusion: According to this whole population based study from Hungary, the incidence of lower limb major amputation is high with no change over the past 9 years. An explanation for this remains to be determined, as the traditional risk factors in Hungary do not account for it. The characteristics of major amputation (the rate of primary amputation, the ratio of below to above knee amputation and the age of the affected population) underline the importance of screening, early detection, improved vascular care and an optimal revascularization policy. Standardization and validation of amputation detection methods and reporting is essential.
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INTRODUCTION

Lower extremity amputation is one of the most devastating consequences of peripheral arterial disease (PAD). Morbidity and mortality data related to this procedure show exceptionally poor results.[1,2] Besides the loss of quality of life in many domains, lower limb amputation has a significant and complex impact on health expenditure.[3,4] All these aspects underline the importance of assessing PAD related lower limb amputation.

Prospective observational studies have limited value in the determination of the incidence of amputation. Inadequate patient enrolment due to expense, insufficient observation time allowing for the assessment of short-term effects only, selection bias in the sample, and low external

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validity are the main shortcomings.[5,6] Analysis of administrative data records (disease and procedure codes, and repeat pharmaceutical prescriptions) is important in the field of amputation. Re-using these data reduces the cost and inefficiencies associated with clinical research. The available data allow for; the examination of more potential confounding variables, exploration of rare occurrences, the study of long-term consequences, application of more advanced statistical methods, and development of data mining techniques.[5] This technique has the potential to analyse andassess regional,[7] national,[8–12] or international trends[13,14] in amputation.

The published data of the incidence of PAD related lower extremity amputation show wide variability.[14] Amputation trends also vary, with a decline in the USA,[15] Italy,[10] Sweden,[16] Germany,[17] and Finland,[18] steadiness in the Republic of Ireland[8] and an increase (for type 2 diabetes related amputation) in Spain[9] and England.[11]

Making comparisons is difficult not only due to the heterogeneity of the studied population, but also because of variations in the reporting methods. In interpreting the amputation incidence figures, many potential pitfalls need to be taken into account.[19]

The aim of this study was to determine the temporal trend of major lower limb amputation associated with peripheral arterial disease in the entire Hungarian population over a nine year period.

MATERIALS AND METHODS

Database

The HUNgarian VASCular DATA (HUNVASCDATA) project is based on the analysis of the health care administrative data for the whole Hungarian population.

The raw data for analysis originated from every outpatient and inpatient medical encounter and repeat pharmaceutical prescriptions during the observational period. The expense claims related to these events are electronically collected for the single health care financer (the National Health Insurance Fund) in a data warehouse architecture. The claim data are transferred and converted for analytical purposes to a governmental organization that is responsible for the dissemination and analysis of health care related data, supporting governmental health care decision makers. The data are stored in the form of a relational database structure (ORACLE) with the potential of performing different query algorithms. The HUNVASCDATA project used this database in close cooperation with the previously mentioned governmental organization by developing disease and procedure specific data extraction algorithms resulting in the analytical file. Data extraction was based on the International Classification of Diseases, tenth revision (ICD-10) and International Classification of Procedures in Medicine (ICPM) codes.

In contrast to the insurance claim file, the identity of patients was not disclosed because of the application of an insurance number encryption algorithm. This process ensured patient anonymity and, simultaneously generated a unique record for each health care beneficiary. With the lack of identifiable individual data, Institutional Review Board (IRB) approval was not required. The research was conducted according to the Act XLVII of 1997 on the Management and Protection of Healthcare and Related Personal Data in Hungary.

Patient data

Pre-defined health care administrative data were used in a patient population with a history of major lower extremity amputation over the observational period of 2004–2012. Cases were defined as events with any lower extremity amputation above the ankle (ICPM 58470—crural, 58480—femoral). To exclude amputations due to causes other than PAD, amputations associated with trauma or bone/skin malignancy were omitted. With the aim of presenting the total burden of major amputation, repeat amputations were also included in the analysis, but stump revisions (ICPM 58500) were not. The presence of comorbidity, vascular events, and amputation history were also identified by ICD-10 and ICPM codes. Primary amputation was defined as a major amputation without any lower limb revascularization (bypass surgery, endovascular) procedure carried out in the preceding one year. To be able to evaluate the preceding history (comorbidity and vascular events) of major amputation, amputations in the first year of the study period were excluded. Several populations at risk of major amputation were defined, including patients affected by diabetes, older patients (age over 65 years), previous minor and major amputees, and patients with a lower limb revascularization history prior to major amputation. There are different algorithms for the detection of diabetes from health care administrative data, depending on the availability of information.[20,21] In this investigation, subjects were considered diabetic if there were two ambulatory care claims in a 2 year period, or one hospital discharge claim using diabetes mellitus specific ICD-10 codes (E10–E14). This algorithm was complemented with the repeat antidiabetic drug prescription data available for a limited period (2010–2012). Diabetes detection was performed at the time of the major amputation event and during the preceding observational period. For the reference diabetic population, the average of diabetes prevalence data biannually reported by the Hungarian Central Statistics Office was used.[22]

Statistical methodology

Demographic characteristics, comorbidities, and the vascular history of the amputees are presented as proportions. Age and sex specific major amputation incidences were calculated using population counts on 1 January each year, obtained from the Hungarian Central Statistics Office.[23] Crude incidences were calculated annually and for the whole period, with 95% confidence intervals for the latter.

To account for both the changing age and sex structure and to make valid international and inter-year comparisons

Table 1. Demographics and clinical characteristics of major amputees.

Number of major amputations	38,200
Number of subjects	32,084
Male/female (%)	65/35
Age (mean year $\pm$ SD)	63.9 $\pm$ 11.5
Diabetes mellitus (%)	50.4
Renal replacement therapy (%)[a]	3
Carotid revascularization in history (%)[a]	1.5
Stroke in history (%)[a]	11.7
Coronary revascularization in history (%)[a]	3.7
Myocardial infarction in history (%)[a]	4.5
Previous lower limb revascularization (%)[a,b]	36.5
Primary amputation (%)[a,c]	71.5
Minor amputation in history (%)[a]	29

[a] In order to ensure at least 1 year of previous history for analysis, major amputations performed in 2004 were excluded from the calculation (number of remaining cases is 33,989).
[b] Detected any time in the whole observational period prior to major amputation.
[c] Defined as major amputation without any detected lower limb revascularization procedure in the preceding year prior to major amputation.

possible, epidemiological standardization[24] was needed. Direct standardization was chosen using different reference populations: (a) population structure of the first investigated year, and (b) external standard population. The first approach is more straightforward to compare different years within the same country; the second is preferable for international comparisons. As an external reference, the European Standard Population (ESP) 2013[25] was chosen. The age composition of the Hungarian population together with these reference populations were scaled to match the Hungarian population in 2004.

Calculations were performed under R software package version 3.0.2 (R Core Team, 2014) and STATA software package version 12.0 (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP) using a custom script that is available from the corresponding author on request.

RESULTS

76,798 lower limb amputation performed over the observational period of nine years (2004—2012) were identified. In the analysis, major amputation cases (38,200 procedures) were the focus. The affected population consisted of 32,084 amputees. The demographics and clinical characteristics of the population that underwent a major amputation are shown in Table 1. Major amputations as repeated events occurred in 15%, resulting in the loss of both lower extremities in 13.9%. The proportion of below knee amputation was 27%. The primary amputation rate was 71.5%. Age and sex had a profound influence on the incidence of major amputation in every year (Fig. 1).

After external direct standardization to ESP 2013, the annual sex specific and total incidences are shown in Table 2. The annual incidences of lower limb major amputation were more than twice as high in males as females.

The annual crude and age adjusted values of lower limb major amputation incidences (2004—2012) are shown in the whole population and in the sex disaggregated population in Fig. 2. While the adjusted incidences do exhibit year on year fluctuation, their erratic nature and the largely overlapping confidence intervals[26] indicate that there is no long = term trend.

No trend in the incidence of major amputation in the elderly, after a minor or major amputation, or after a previous lower limb revascularization was seen; therefore, major amputation incidences are shown for the whole period as a single aggregated value (on person time basis) (Table 3). The diabetes related incidence of major amputation was seven times higher than in the general population and 15 times higher than in non-diabetic subjects. If diabetes status was only checked at the major amputation event it resulted in a 5% decrease in diabetes related amputation incidence compared with diabetes detection in the whole period preceding amputation. In elderly patients, the incidence was four times higher than in the general population. Any antecedent lower limb procedure (minor or major amputation, or revascularization) was associated with a markedly increased risk for subsequent major amputation. In these cases, the incidence was higher by two orders of magnitude (100—180 fold) than in the general population.

DISCUSSION

This study, in the context of the HUNVASCDATA project, provides the first whole-population based data of PAD associated major lower limb amputation in Hungary.

Before drawing any inferences from the data, the accuracy of the health care administrative databases as the prevailing source of information in amputation research has to be addressed. There are more dimensions to the validity of health care administrative data such as completeness, correctness, concordance, plausibility, and currency.[27] The database is considered to be acceptably complete, in the sense that it covers almost the whole population in Hungary, and the National Health Insurance Fund is the single financial source of health care service, covering all beneficiaries. The private sector can be ignored, especially in the field of amputation. The health care data primarily serve as the basis for all expenditure for medical services in Hungary. The data record, transfer, and analysis are performed according to legal regulation and as a consequence they are subject to close data quality control by cross tabulation, regular claim supervision, and local inspection. Amputation as a procedure is easily defined, and the error of commission (surplus coding) is low. Error of omission (lack of coding) was not assessed, but underestimation is possible. Health care administrative data, using critical limb ischemia (CLI) specific diagnoses showed 75% sensitivity for CLI identification. If CLI specific procedure codes (amputation, revascularization) were added, the sensitivity was even higher (92%).[28] For amputation detection, another publication reported a sensitivity value of 94.4%,[29] which is similar or superior to other disease conditions.[28] As for the

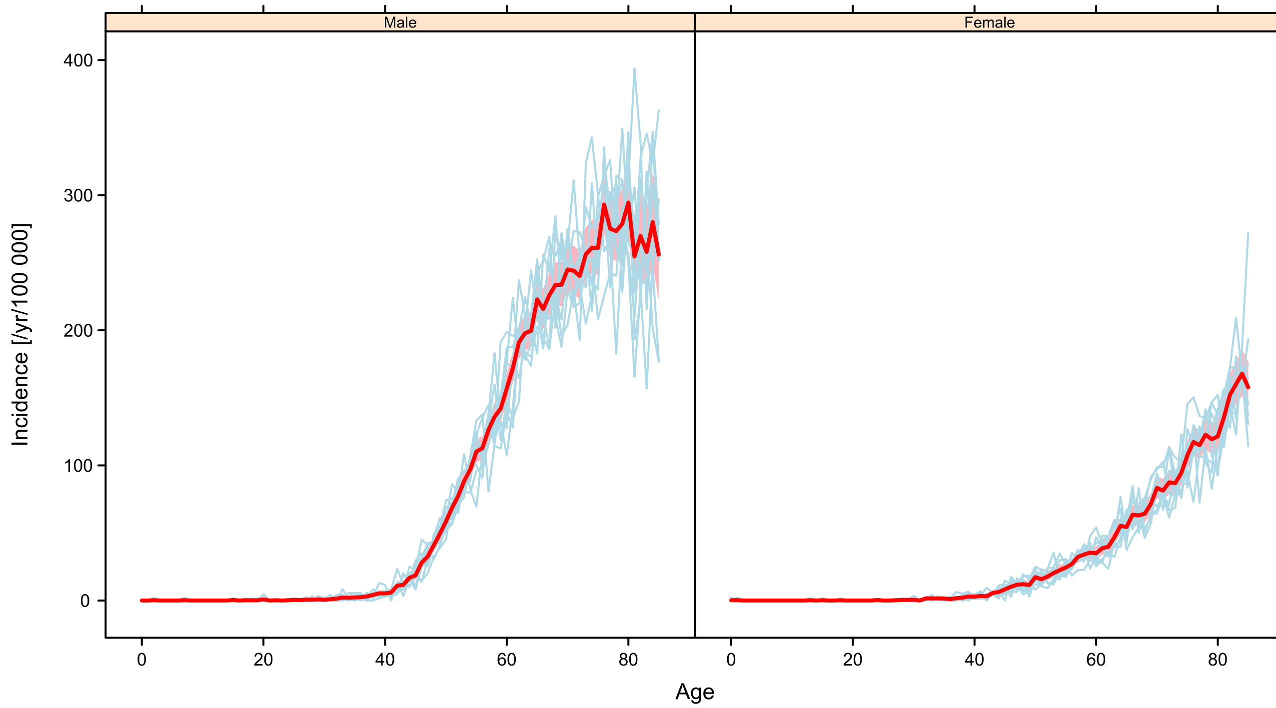

Figure 1. Age- and sex-specific incidences of major lower limb amputations in Hungary (2004—2012). Thin blue lines show the incidences individually for each investigated year (2004—2012). Thick red line is the overall incidence calculated from the whole 2004—2012 period. Pink shading depicts the 95% confidence interval for these latter age- and sex-specific incidence curves.

comorbidity, the application of disease classification codes (ICD) alone leads to grater uncertainty;[30] therefore, a more complex algorithm of ICD codes for case detection, like the definition of diabetes, was applied. This kind of approach is considered to be valid.[31]

In summary it is believed that the validity of the HUN-VASCDATA is similar to other reports on amputation trends, but international harmonization of methods is greatly needed in this evolving field.

Internationally reported amputation incidence data show wide variability. In order to define the basis for comparison the individual reports in the meta-analysis of Moxey et al.were considered.[14] They collected all publications focusing on lower limb amputation in the UK and worldwide between 1989 and 2010. Six more recent European reports were added to the national estimates of major amputation incidences.[9,10,17,18,32,33] According to these sources, the incidence data ranged from 3.6 to $58.7/10^5$ (average $13.07/10^5$ of 19 reports) in the total population. Although this wide range is partly due to different calculation methods, there is no doubt that the Hungarian amputation incidence statistics ($42.3/10^5$, as a single aggregated value) are especially high, being more than three times that of the average published.

Table 2. Lower limb major amputations incidences (rates per 10^5 persons) after direct standardization to ESP 2013.

Year	Male	Female	Total
2004	107.3	47.8	69.3
2005	93.6	46.2	64.1
2006	112.3	43.9	68.2
2007	101.6	41.1	63.2
2008	104.3	42.2	64.8
2009	101.8	41.2	63.6
2010	112.4	45.3	69.8
2011	103.1	41.9	64.5
2012	106.1	41.3	64.7

The population that underwent major amputation was somewhat younger in contrast to other European reports. The extent of the difference is similar to the difference in life expectancy,[34] reflecting general health conditions.

A striking difference was detected between men and women regarding amputation incidence in all age groups. The observed male dominance in major amputation incidence is in accord with the results of a recent meta-analysis showing that the diabetes related amputation risk is 50% higher in males.[35] No clear explanation is given for this. The role of a different barrier to health care access, reluctance to seek medical consultation, and more social expectation in a job, may account for this gender difference.[35]

A high incidence was noted in other predefined subgroups, such as diabetic and elderly patients. Diabetes related major amputation showed a 15 fold increase compared with non-diabetic subjects. A value of $318/10^5$ can be considered high compared with other countries.[14] However, there is a methodological issue in reporting diabetes related amputation. In the calculation of incidence (as a fraction), both the definition of the numerator (diabetes related amputation) and the denominator (diabetes prevalence) are uncertain.

In some publications,[8,11] amputation was considered to be diabetes related if at the amputation event diabetes

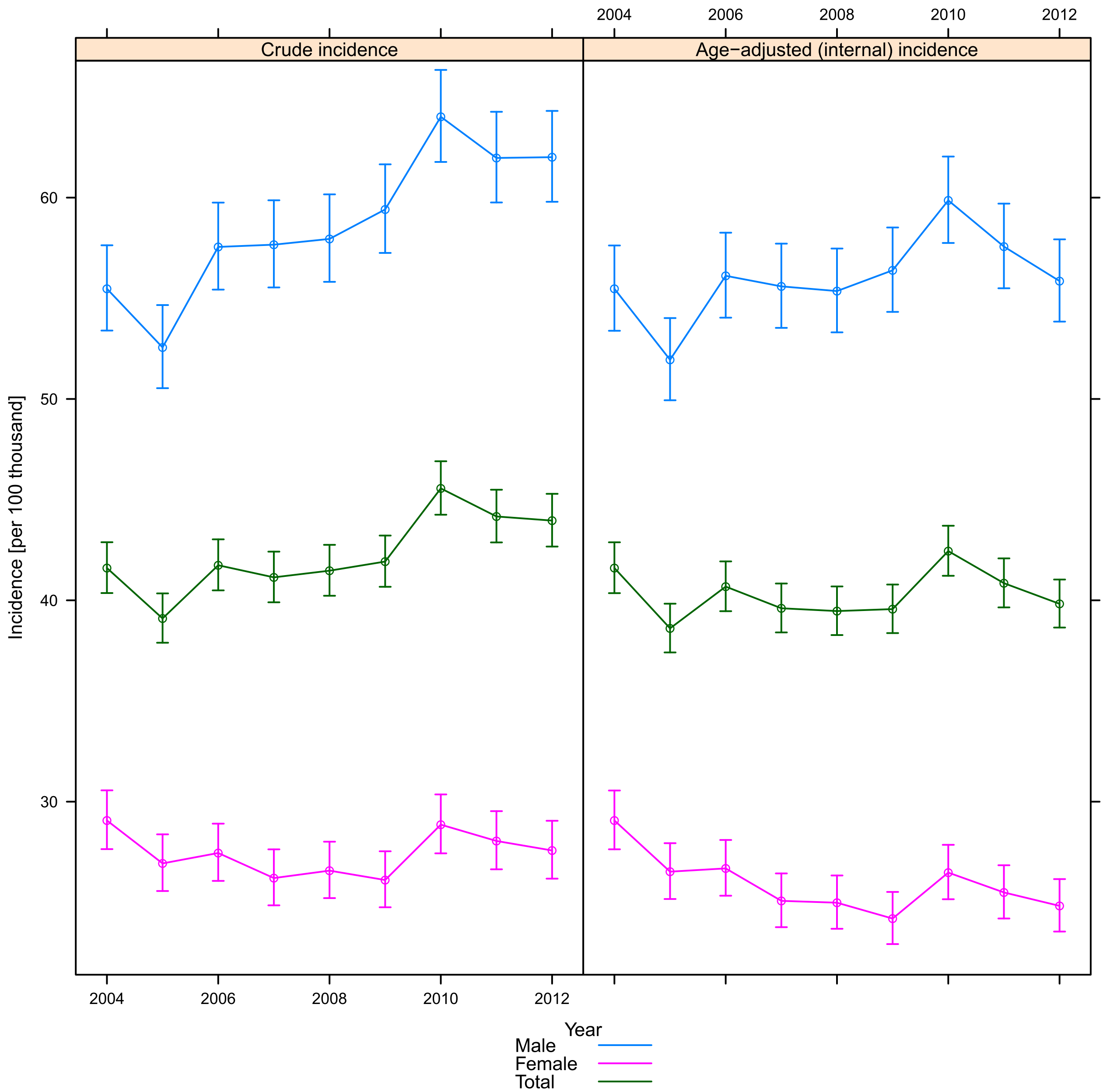

Figure 2. Crude and age-adjusted incidences of lower limb major amputations by year, 2004—2012.

Table 3. Crude lower limb major amputations incidences (rates per 10^5 persons) in different patients groups, calculated for the whole observational period.

Group	Exposure (person-years)	Events	Incidence (crude), with 95% CI
General population	90,274,308	38,200	42.29 (41.87—42.7)
>65 yrs	13,727,535	22,218	161.85 (159.73—163.99)
Diabetic	6,559,808	20,855	317.92 (313.63—322.27)
Not diabetic	83,714,500	17,345	20.72 (20.41—21.03)
Prior major amputation	14,411,419	5,773	4005.9 (3905.5—4108.7)
Prior minor amputation	12,584,646	9,859	7843.4 (7686.6—7984.3)
Prior lower limb revascularization	24,194,507	9,673	3998 (3920.4—4077.0)

specific codes were also used. However, under reporting of amputation in diabetics at the time of hospital discharge may lead to a decrease in the diabetes related amputation incidence. In an Italian report, it reached 10%,[10] in the data here, this effect was less significant (5%). To avoid this, a complex definition for diabetes detection was used covering the whole period preceding amputation.

As for the denominator, although there are several reports about the increase in the prevalence of diabetes, using these data without estimating their robustness and scientific merit can result in a potential bias by decreasing the amputation incidence fraction. For this reason, an average (constant number) of the diabetes prevalence data reported in primary care in Hungary was used.[22] The amputation literature is not uniform regarding this issue.

No changes in the trend of amputation in the whole population or in several predefined risk populations were detected over the observational period (2004–2012). The constantly high incidence of major amputation is in contrast with other national reports.[10,15–17]

When searching for potential explanations, the pattern of traditional risk factors for PAD (smoking, age, sex, and diabetes) and the role of vascular care must be considered.

The Hungarian population shows aging similar to other European countries. Between 2004 and 2012 there was a 10% increase from 15.5% to 17.5% in the proportion of the older population (age above 65 years),[36] which is similar to European trends.[37] Based on this fact, the crude amputation incidence data described here are similar to other published results in this respect. Nevertheless, the distracting effect of age and sex distribution on lower limb amputation incidence can be eliminated by direct standardization to a reference population, as was done in this study with ESP 2013. The use of this technique is not common in the amputation literature; however, mass migration[38] and aging may profoundly influence the incidence data by changing the demographic composition of local populations. Recognition of the importance of the changing composition of the European population led to revision of the previous version of ESP data in 2013.[39] Geographical coverage of ESP-2013 was agreed to be the EU 27 and EFTA countries. Eurostat's task force determined that it was unnecessary to separate the new ESP by sex in order to avoid a more complex system that is not required for most comparative uses.[39] Nevertheless, in the case of lower limb amputation incidence, gender is a very influential factor. Therefore, disaggregation by sex can lead to greater accuracy and a better reflection of reality. In order to meet these two expectations and to show internationally comparable data, the overall and the sex specific standardized major amputation incidence rates have been reported (Table 2). These data are suitable for international comparison with other cohorts with the same definitions.

According to OECD data,[40] Hungarian smoking data are not different in comparison to EU-27 (daily smoking rate, 26.5% vs. 23%; decline in smoking in the past 10 years 12.4% vs. 16.3%). Based on these data, smoking is probably not a dominant factor in explaining the high amputation incidence data in Hungary. However, according to WHO data, the prevalence of smoking is higher in men than in woman in Hungary (35% vs. 27%) and could contribute to the gender differences in the amputation rate.[41]

Diabetes is certainly one of the most influential factors regarding amputation incidence. In this amputee population diabetes was detected in 50.4%, which is in accord with the results other amputation reports.[18] According to OECD statistical data, the Hungarian diabetes prevalence data (6.2%) are close to the European 22 average (6.4%).[42] Based on these comparisons, it is assumed that diabetes prevalence alone does not account for the high major amputation rates in Hungary.

Summing up, the data about the pattern of traditional PAD risk factors in Hungary does not provide a clear explanation for the high and constant major amputation rate. The high primary amputation rate (71.5%), the low below to above knee amputation ratio (0.3), and the younger age of the affected population indicate that vascular health care provision may provide an explanation.

The most obvious indicator, the primary amputation rate, seems to be exceptionally high. A US Medicare based study found that the rate was 33% for the critical limb ischemia affected population.[43] In another publication studying critical limb ischemia, the overall rate of primary amputation was 54%, ranging from 42% to 68%.[44] However, interpretation of the Hungarian data on primary amputation is problematic. Firstly, in depth comparison is not possible due to a lack of available published data in reports about amputation. Secondly, the extent to which the indication for primary amputation in the Hungarian population had met the criteria for unreconstructable arterial disease could not be assessed. A Medicare claims based report showed that the rate of any pre-amputation arterial testing (Doppler measurement, vascular imaging) was 68.4%.[45] Although no Hungarian or European data are available for comparison, this single observation cautions against over-interpretation of the primary amputation rate.

All these points may lead to the assumption that major amputation incidence is closely related to the complexity of the vascular care service. The question cannot be reduced to one factor, such as access to vascular surgery, as a high proportion of patients with vascular disease in Hungary have access to open or endovascular surgery. According to a rough estimate by the Hungarian Society of Angiology and Vascular Surgery, the number of vascular surgeons per capita is 1/110.000, which is in the range (1/107.000–1/147.000) of other reports from USA, France, and the UK.[46] The high amputation rate is probably related to a failure at one or more of the many steps in the patient pathway, including the late recognition of PAD, the lack of PAD specific screening programs, delayed admission for vascular care, the existence of medically underserved regions, and the suboptimal rate of revascularization (surgical or endovascular). The potential impact of these factors should be analyzed in the future.

CONCLUSIONS

The HUNVASCDATA study is the first to present a detailed, whole-population based analysis of national lower limb major amputation trends in Hungary. High and constant incidence data were detected, that are presumably related to the capacity and organization of the health care service. An improvement in screening and access for revascularization is badly needed. Comparing these data with other national amputation incidence data is problematic because of different reporting methods. Using the ESP 2013 as a tool for external standardization of incidence data is recommended in order to ensure international comparability. Analysis of the whole population health care administrative data increases knowledge of PAD epidemiology; however, the accuracy of algorithms and classifications causes uncertainty and validation studies are needed.

CONFLICT OF INTEREST

None.

FUNDING

None.

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